

- E1
- 4 (i) transforming a mouse ES cell with a first DNA construct encoding
5 a first indicator component under the control of a promoter having restricted expression
6 in a mouse;
7 (ii) transforming the cell of (i) or a descendent of the cell by operably
8 integrating into the cell's genome, a second DNA construct comprising DNA encoding a
9 second indicator component not operably linked to a transcription control element;
10 (iii) producing tissue or specialized cells from the cell of (ii); and
11 (iv) monitoring the tissue or specialized cells of (iii) for a detectable
12 indicator resulting from both the first and second indicator components indicative of
13 integration of the second DNA construct into a gene having restricted expression.

- E2
- 1 ~~5~~ ~~6~~ (Twice Amended) The method of claim 1 which additionally
2 comprises isolating DNA endogenous to the mouse ES cell or descendent thereof which
3 flanks the second DNA construct integrated into a gene having restricted expression.

- ~~E3~~
SUB
F1
- 1 12. (Twice Amended) The combination of:
2 (i) a DNA construct for integration into the genome of an eukaryotic cell
3 comprising a sequence encoding a first indicator component under the control of a
4 promoter having restricted expression; and
5 (ii) a DNA construct for integration into the genome of a eukaryotic cell,
6 comprising in the 5' to 3' direction, a splice acceptor, a sequence encoding a second
7 indicator component not operably linked to a transcription control element, and an
8 optional IRES, wherein expression of both the first and second indicator components in
9 said cell is detectable, and wherein in the absence of either indicator component, there is
10 no detectable indicator.

- E4
- 1 ~~3~~ ~~13~~. (Twice Amended) A mouse ES cell or descendent thereof,
2 transformed by the combination of DNA constructs of claim ~~12~~ ¹.

1 ~~12~~ 18. (Twice Amended) A method of producing mouse tissue or
2 specialized cells comprising a detectable indicator associated with a target gene having
3 restricted expression, which comprises:
4 (i) transforming a mouse ES cell with a first DNA construct encoding
5 a first indicator component under the control of a promoter having restricted expression
6 in a mouse;
7 (ii) transforming the cell of (i) or a descendent of the cell by
8 integrating into the cell's genome, a second DNA construct comprising DNA encoding a
9 second indicator component not operably linked to a transcription control element;
10 (iii) producing tissue or specialized cells from the cell of (ii); and
11 (iv) selecting tissue or specialized cells of (iii) by the presence of a
12 detectable indicator resulting from both the first and second indicator components.

1 ~~13~~ 19. (Twice Amended) A method of producing a mouse comprising a
2 detectable indicator associated with a target gene having restricted expression, which
3 comprises:
4 (i) transforming a mouse ES cell by integrating into the cell's genome,
5 a first DNA construct encoding a first indicator component under the control of a
6 promoter having restricted expression;
7 (ii) transforming the cell of (i) or a descendent of the cell by
8 integrating into the cell's genome, a second DNA construct comprising DNA encoding a
9 second indicator component not operably linked to a transcription control element;
10 (iii) selecting transformed cells of (ii);
11 (iv) introducing selected cells of (iii) into a mouse host embryo;
12 (v) implanting the host embryo of (iv) into a pseudopregnant mouse;
13 (vi) maintaining the mouse of (v) while offspring develops to term
14 from the host embryo; and